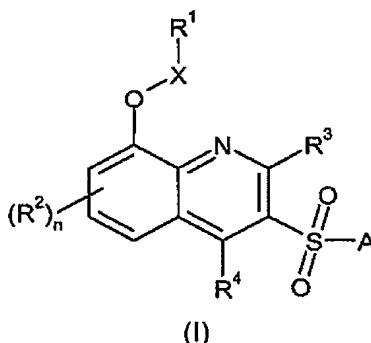


3-((HETERO)ARYLSULFONYL)-8-(AMINOALKYL)OXYQUINOLINES AS 5-HT₆ RECEPTOR ANTAGONISTS FOR THE TREATMENT OF CNS DISORDERS

This invention relates to novel quinoline compounds having pharmacological activity, to processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements. WO 00/42026 (Novo Nordisk) describes a series of quinoline and quinoxaline compounds for use as GLP-1 agonists. WO 04/000828 (Biovitrum AB) describe a series of bicyclic sulfone or sulfonamide compounds which are claimed to be useful in the treatment or prophylaxis of a 5-HT₆ receptor related disorder. WO 00/71517 describes a series of phenoxypropylamine compounds as 5-HT_{1A} receptor antagonists which are claimed to be useful as anti-depressants.

A structurally novel class of compounds has now been found which also possess antagonist potency for the 5-HT₆ receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

R¹ represents a group of formula -NR^aR^b or a nitrogen containing heterocyclyl group optionally substituted by one or more (eg. 1 to 4) C₁₋₆ alkyl groups;

X represents a bond, -(CR^cR^d)-, -(CR^cR^d)-(CR^eR^f)-, -(CR^cR^d)-(CR^eR^f)-(CR^gR^h)- or -heterocyclyl-, wherein said heterocyclyl group may be optionally substituted by one or more (eg. 1 to 4) C₁₋₆ alkyl groups; such that when R¹ represents -NR^aR^b, X does not represent a bond nor -(CR^cR^d)-;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h independently represent hydrogen or C₁₋₆ alkyl;

R² represents halogen, cyano, -CF₃, -CF₃O, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl or a group -CONR⁵R⁶;

n represents 0 to 3;

R³ and R⁴ independently represent hydrogen, halogen, cyano, -CF₃, -CF₃O, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl or a group -CONR⁵R⁶;

R⁵ and R⁶ independently represent hydrogen or C₁₋₆ alkyl or together with the N atom to which they are attached may be fused to form a 5- to 7- membered nitrogen containing aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

A represents an -aryl, -heteroaryl, -aryl-aryl, -aryl-heteroaryl, -heteroaryl-aryl or -

5 heteroaryl-heteroaryl group;

wherein said aryl and heteroaryl groups of A may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are

selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁₋₆ alkoxy,

10 arylC₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxyC₁₋₆ alkyl, C₃₋₇ cycloalkylC₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆ alkylsulfonylC₁₋₆ alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₆ alkyl, C₁₋₆

alkylsulfonamido, C₁₋₆ alkylamido, C₁₋₆ alkylsulfonamidoC₁₋₆ alkyl, C₁₋₆ alkylamidoC₁₋₆ alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁₋₆ alkyl, arylcarboxamidoC₁₋₆

15 alkyl, aroyl, aroylC₁₋₆ alkyl, arylC₁₋₆ alkanoyl, or a group CONR⁷R⁸ or SO₂NR⁷R⁸, wherein R⁷ and R⁸ independently represent hydrogen or C₁₋₆ alkyl or R⁷ and R⁸ together with the

nitrogen atom to which they are attached may form a nitrogen containing heterocyclyl or heteroaryl group;

or solvates thereof.

20

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. In one embodiment the alkyl moieties are C₁₋₄ alkyl, eg. methyl or ethyl.

25 The term 'cycloalkyl' means a closed 4- to 8- membered non-aromatic ring, for example cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or cyclooctyl.

The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

30

The term "aryl" includes single and fused rings for example, phenyl or naphthyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from

35 oxygen, nitrogen and sulfur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused bicyclic aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl,

40 benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule

via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur fused to a benzene or monocyclic heteroaryl ring (referred to as fused rings); or an 8-membered bicyclic saturated nitrogen containing aliphatic ring. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, diazepanyl, azepanyl, dihydroimidazolyl, tetrahydropyranyl, tetrahydrothiapyranyl and tetrahydrofuranyl. Suitable examples of fused rings include dihydroindolyl, dihydroisoindolyl, tetrahydroquinolyl, tetrahydrobenzazepinyl and tetrahydroisoquinolyl. A suitable example of an 8-membered bicyclic saturated nitrogen containing aliphatic ring is azabicyclo[2.2.2]octyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "nitrogen containing heteroaryl" is intended to represent any heteroaryl group as defined above which contains a nitrogen atom

The term "nitrogen containing non-aromatic heterocyclic ring" is intended to mean a 5 to 7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 nitrogen atoms and further optionally interrupted by an oxygen or sulphur atom. Suitable examples of such rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, diazepanyl, azepanyl and dihydroimidazolyl.

The term "nitrogen containing aromatic heterocyclic ring" is intended to mean any 5 to 7 membered aromatic monocyclic ring containing 1 to 3 nitrogen atoms and further optionally interrupted by an oxygen or sulphur atom. Suitable examples of such rings include oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

In one embodiment, R^1 represents a group of formula NR^aR^b , wherein R^a and R^b independently represent hydrogen or a methyl group.

In one embodiment, R^1 represents a 5- to 8-membered nitrogen containing heterocyclyl group optionally substituted by one or more C_{1-3} alkyl groups.

In one embodiment, R^1 represents NR^aR^b , wherein R^a and R^b are independently hydrogen or methyl; or a nitrogen containing heterocyclyl group selected from pyrrolidinyl, piperidinyl, morpholinyl, azabicyclo[2.2.2]oct-3-yl or azepinyl any of which may be optionally substituted by methyl or isopropyl.

- 5 In one embodiment, X represents a bond, $-(CR^cR^d)-$, $-(CR^cR^d)-(CR^eR^f)-$, $-(CR^cR^d)-(CR^eR^f)-(CR^gR^h)-$ or a tetrahydrofuranyl ring; such that when R^1 represents NR^aR^b , X does not represent a bond nor $-(CR^cR^d)-$.

In one embodiment, X represents a bond, $-CH_2-$, $-CH_2-CH_2-$ or $-C(H)(Me)-C(H)(Me)-$.

- 10 In one embodiment, R^1-X- represents $-(CH_2)_2-N(Me)_2$, $-CH_2-(1-methyl-2-pyrrolidinyl)$, $-CH_2-(2-pyrrolidinyl)$, $-(CH_2)_2-(1-pyrrolidinyl)$, $-3-pyrrolidinyl$, $-C(H)(Me)-C(H)(Me)-N(Me)_2$, $-(CH_2)_2-(1-piperidinyl)$, $-(CH_2)_2-(4-morpholinyl)$, $-azabicyclo[2.2.2]oct-3-yl$, $-(CH_2)_3-(1-piperidinyl)$, $-(CH_2)_2-(hexahydro-1H-azepin-1-yl)$, $-4-amino-tetrahydro-3-furanyl$, $-4-dimethylamino-tetrahydro-3-furanyl$, $-3-piperidinyl$, $-4-piperidinyl$, $-1-methyl-3-pyrrolidinyl$, $-1-methyl-4-piperidinyl$, $-CH_2-(azabicyclo[2.2.2]oct-2-yl)$, $-1-methyl-3-piperidinyl$, $-CH_2-(3-morpholinyl)$, $-CH_2-(1-methylethyl-2-pyrrolidinyl)$ or $-C(H)(Me)-CH_2-N(Me)_2$.

In one embodiment, R^1-X- represents $-(CH_2)_2-N(Me)_2$, $-CH_2-(1-methyl-2-pyrrolidinyl)$, $-CH_2-(2-pyrrolidinyl)$, $-(CH_2)_2-(1-pyrrolidinyl)$, $-3-pyrrolidinyl$ or $-C(H)(Me)-C(H)(Me)-N(Me)_2$.

- 20 In one embodiment R^a , R^b , R^c , R^d , R^e , R^f , R^g and R^h independently represent hydrogen or a methyl group.

In one embodiment, R^a and R^b both represent C_{1-6} alkyl (eg. methyl).

In one embodiment, R^c and R^d either both represent hydrogen or one represents hydrogen and the other represents C_{1-6} alkyl (eg. methyl).

- 25 In one embodiment, R^e and R^f either both represent hydrogen or one represents hydrogen and the other represents C_{1-6} alkyl (eg. methyl).

In one embodiment, n represents zero.

In one embodiment, n represents 1 and R^2 represents halogen.

In one embodiment, n represents 1 and R^2 represents chlorine.

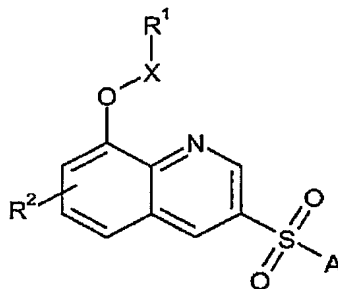
- 30 In one embodiment, R^3 and R^4 both represent hydrogen.

In one embodiment, A represents $-aryl$ (eg. phenyl) optionally substituted by one or more halogen (eg. chlorine) atoms or $-heteroaryl$ (eg. pyridyl).

In a further embodiment, A represents $-aryl$ (eg. phenyl) optionally substituted by a halogen (eg. chlorine).

- 35 In a further embodiment, A represents unsubstituted phenyl.

In yet a further embodiment there is provided a compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein:

- 5 R^1 represents a group of formula NR^aR^b , or a nitrogen containing heterocyclyl group selected from pyrrolidinyl, piperidinyl, morpholinyl, azabicyclo[2.2.2]oct-3-yl or azepinyl any of which may be optionally substituted by methyl or isopropyl; X represents a bond, $-(CR^cR^d)-$, $-(CR^cR^d)-(CR^eR^f)-$, $-(CR^cR^d)-(CR^eR^f)-(CR^gR^h)-$ or a tetrahydrofuranyl ring; such that when R^1 represents NR^aR^b , X does not represent a
- 10 bond nor $-(CR^cR^d)-$;
 R^a , R^b , R^c , R^d , R^e , R^f , R^g and R^h independently represent hydrogen or a methyl group;
 R^2 represents hydrogen or halogen; and
A represents phenyl optionally substituted by one or more halogen atoms.
- 15 Compounds according to the invention include examples E1-E27 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be

20 pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or

25 naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention

30 includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

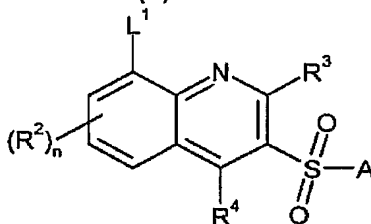
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these

35 stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or

any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

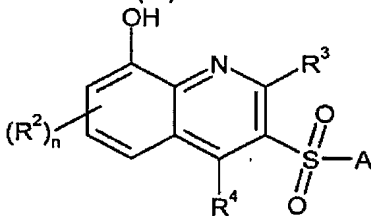
(a) reacting a compound of formula (II)



(II)

or an optionally protected derivative thereof, wherein R^2 , R^3 , R^4 , n and A are as defined above and L^1 represents a leaving group such as a halogen atom or a trifluoromethylsulfonyloxy group;
with a compound of formula R^1 -X-OH or an optionally protected derivative thereof, wherein R^1 and X are as defined above, and optionally thereafter removing any protecting groups; or

(b) reacting a compound of formula (III)



(III)

or an optionally protected derivative thereof; wherein R^2 , R^3 , R^4 , n and A are as defined above;
with a compound of formula R^1 -X- L^2 or an optionally protected derivative thereof, wherein R^1 and X are as defined above and L^2 represents a leaving group such as a halogen atom or a methylsulfonyloxy group, and thereafter optionally removing any protecting groups; or

(c) reacting a compound of formula (III) as defined above or an optionally protected derivative thereof, with a compound of formula R^1 -X-OH as defined above or an optionally protected derivative thereof, and thereafter optionally removing any protecting groups;

(d) deprotecting a compound of formula (I) which is protected;

(e) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

5 Process (a) typically comprises the use of basic conditions and may be conveniently carried out using a compound of formula (II) where L^1 represents a fluorine atom and an alkali metal salt of a compound of formula R^1-X-OH in a suitable solvent such as *N,N*-dimethylformamide or dimethyl sulfoxide. The alkali metal salt of a compound of formula R^1-X-OH may be generated using a suitable alkali metal hydride such as sodium
10 hydride. Alternatively, process (a) may be conveniently carried out using a compound of formula (II) where L^1 represents an iodine atom, in the presence of a base such as cesium carbonate and a suitable copper salt such as copper (I) iodide in a suitable solvent such as toluene. Process (a) may be optionally carried out at elevated temperature, e.g. 90 – 110 °C.

15 Process (b) typically comprises the use of basic conditions and may be conveniently carried out either (i) using an alkali metal salt of a compound of formula (III), generated using a suitable alkali metal hydride such as sodium hydride, in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran or (ii) using a base such as potassium
20 carbonate in a suitable solvent such as *N,N*-dimethylformamide, acetone or 2-butanone. Process (b) may be optionally carried out at elevated temperature, e.g. reflux temperature or 90 – 110 °C.

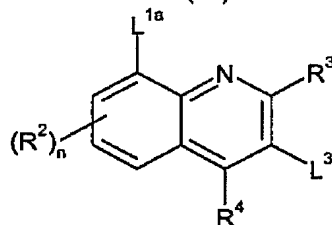
25 Process (c) typically comprises the use of Mitsunobu conditions, using a suitable substituted phosphine such as triphenylphosphine and an appropriate azodicarbonyl reagent such as diethyl diazodicarboxylate in a suitable solvent such as dichloromethane or tetrahydrofuran.

30 In processes (a), (b), (c) and (d) examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive
35 removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic
40 acid. A further amine protecting group includes methyl which may be removed using standard methods for N-dealkylation (e.g. 1-chloroethyl chloroformate under basic conditions followed by treatment with methanol).

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, reductive alkylation, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, *N*-dealkylation of a compound of formula (I) wherein R^a represents an alkyl group to give a compound of formula (I) wherein R^a represents hydrogen. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion.

Compounds of formula (II) may be prepared as described in WO 03/080580.

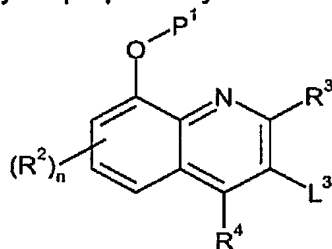
Compounds of formula (II) wherein L^1 represents a fluorine or chlorine atom may be prepared by reacting a compound of formula (IV)



(IV)

wherein L^{1a} is a fluorine or chlorine atom, L^3 is a suitable leaving group such as an iodine atom, and R^2 , R^3 , R^4 , and n are as defined above; with a compound of formula $A-SO_2-M$, wherein A is as defined above and M is a metal residue such as sodium or potassium, in the presence of a copper (I) salt, e.g. copper (I) triflate or copper (I) iodide, in a suitable solvent such as dimethyl sulfoxide, anhydrous *N,N*-dimethylformamide or 1,4-dioxane, optionally including a ligand such as *N,N*-dimethyl-ethylene-1,2-diamine and optionally in the presence of a base such as potassium carbonate.

Compounds of formula (III) may be prepared by reaction of a compound of formula (V)

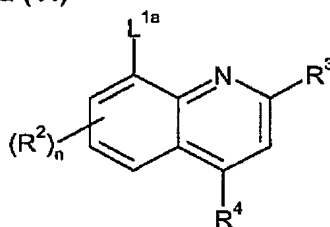


(V)

wherein L^3 , R^2 , R^3 , R^4 , and n are as defined above and P^1 represents a suitable protecting group such as a trialkylsilylethyl group (e.g. trimethylsilylethyl) or a trifluoromethylsulfonyloxy group, with a compound of formula $A-SO_2-M$ as defined above in a manner similar to that used to prepare compounds of formula (II); and thereafter removing the protecting group, eg. when P^1 represents a trialkylsilylethyl group, such

deprotection may typically be carried out using an alkali metal fluoride salt or a tetraalkylammonium fluoride salt (eg. tetrabutylammonium fluoride).

- 5 Compounds of formula (IV) wherein L^3 represents an iodine atom may be prepared by reacting a compound of formula (VI)

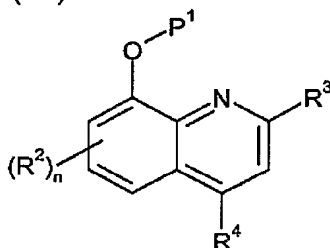


(VI)

wherein L^{1a} , R^2 , R^3 , R^4 and n are as defined above; with an iodinating agent such as *N*-iodosuccinimide in a suitable solvent such as acetic acid.

10

Compounds of formula (V) wherein L^3 represents an iodine atom may be prepared by reacting compounds of formula (VII)



(VII)

- 15 wherein R^2 , R^3 , R^4 , n and P^1 are as defined above; with an iodinating agent such as *N*-iodosuccinimide in a suitable solvent such as acetic acid.

Compounds of formula (V) may also be prepared from compounds of formula (IV) as defined above by reaction with a compound of formula P^1 -OH, wherein P^1 is as defined above, in the presence of a base such as sodium hydride in a suitable solvent such as tetrahydrofuran.

20

Compounds of formula (VI) and (VII) are either known in the literature or can be prepared by analogous methods.

25

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT₆ receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive

30

decline, mild cognitive impairment and vascular dementia), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia (in particular cognitive deficits of schizophrenia), stroke and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

5-HT₆ antagonists have the potential to be capable of increasing basal and learning-induced polysialylated neuron cell frequency in brain regions such as the rat medial temporal lobe and associated hippocampus, as described in WO 03/066056. Thus, according to a further aspect of the present invention, we provide a method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders,
5 injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants,
10 disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for
15 reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for
20 injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be
25 frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be
30 accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60%
35 by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05
40 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than

once a day may be required; and such therapy may extend for a number of weeks or months.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

8-Fluoro-3-iodoquinoline (D1)

15 *N*-Iodosuccinimide (8.1 g, 36.0 mmol, 2 eq.) was added to a solution of 8-fluoroquinoline (2.65 g, 18.0 mmol) in AcOH (13.25 ml, 5 vol). The mixture was stirred and placed in an oil bath which was then heated to 80°C. After 20 hrs 25min the flask was removed from the oil bath and allowed to cool to room temperature. CH₂Cl₂ (13.5 ml) was added, the solution was washed with 10% w/v Na₂SO₃ (aq) (23.5 ml), then with H₂O (13.5 ml) before being concentrated under reduced pressure. The crude product was pre-absorbed on
20 silica and purified via column chromatography, eluting with 19:1 isohexane/EtOAc 1% Et₃N to yield 8-fluoro-3-iodoquinoline (D1) as a white solid (3.46 g, 12.7 mmol, 70%).
¹H NMR (CDCl₃, 400MHz) δ 7.40-7.45 (1H, m, ArH), 7.50-7.52 (2H, m, ArH), 8.58 (1H, t, *J* 1.7 Hz, ArH), 9.09 (1H, d, *J* 2.0 Hz, ArH).

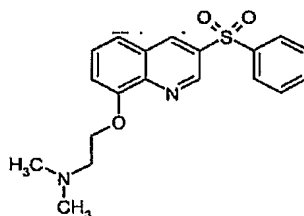
Description 2

8-Fluoro-3-(phenylsulfonyl)quinoline (D2)

25 A flask was charged with copper (I) iodide (70 mg, 0.366 mmol, 0.1eq.), 8-fluoro-3-iodoquinoline (D1) (1.00 g, 3.66 mmol), phenylsulfinic acid sodium salt (1.56 g, 10.98 mmol, 3 eq.) and potassium carbonate (1.01 g, 7.32 mmol, 2eq). DMSO (5 ml) then *N,N'*-dimethylethylene-1,4-diamine (0.078ml, 0.2 eq.) was added, the mixture was stirred and placed in an oil bath which was heated to 90 °C.
30 After heating for 3 ½ hrs the flask was removed from the oil bath and allowed to cool to room temperature. The mixture was filtered and the cake was washed with DMSO (2 x 2 ml), the cake was then slurried with water (4 ml) and filtered, then washed with water (2
35 x 2 ml), sucked dry and further dried in at 50 °C under reduced pressure to yield 8-fluoro-3-(phenylsulfonyl)quinoline (D2) as an off-white solid (0.485 g, 46%).
¹H NMR (CDCl₃, 400MHz) δ 7.54-7.67 (5H, m, ArH), 7.78 (1H, d, *J* 8.3 Hz, ArH), 8.04 (2H, m, ArH), 8.85 (1H, m, ArH), 9.31 (1H, d, *J* 2.0 Hz, ArH).

Example 1a

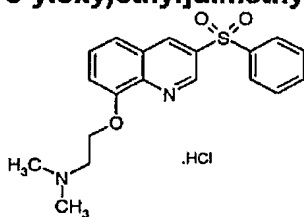
[2-(3-Phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine (E1a)



A round bottom flask was charged with copper (I) iodide (10 mg, 0.05 mmol), cesium carbonate (500 mg, 1.53 mmol), 2-dimethylaminoethanol (68 mg, 0.76 mmol) and 3-phenylsulfonyl-8-iodoquinoline (300 mg, 0.76 mmol) (WO 03/080580). The flask was then purged with argon and toluene (5 ml) introduced. The reaction mixture stirred was heated at reflux for 18 h. The reaction mixture was cooled and filtered. The filtrate was partitioned between dichloromethane (50 ml) and water (50 ml), the organic layer separated, dried over magnesium sulfate and concentrated to a brown paste. This was purified on silica, eluting with a dichloromethane/methanol (0 to 15%) gradient. [2-(3-Phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine (E1a) was obtained as a light brown solid (130 mg, 48%). ¹H NMR (CDCl₃) δ 2.40 (6H, s), 2.96 (2H, t, J = 6.0 Hz), 4.34 (2H, t, J = 6.2 Hz), 7.21-7.25 (2H, m), 7.51-7.56 (4H, m), 8.03 (2H, d, J = 7.1 Hz), 8.77 (1H, d, J = 2.0 Hz), 8.26 (1H, br s).

Example 1b

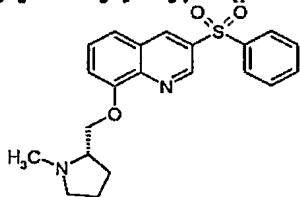
[2-(3-Phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine, hydrochloride (E1b)



The free base was dissolved in methanol and transformed into the hydrochloride salt (E1b) by treating with HCl in Et₂O and stirring for 5 minutes followed by evaporation of the solvent. MS: m/z (M+H)⁺ 357, C₁₉H₂₀N₂O₃S requires 356.

Example 2a

8-([(2S)-1-Methyl-2-pyrrolidiny]methyl)oxy-3-(phenylsulfonyl) quinoline (E2a)

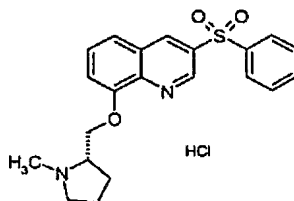


To a suspension of sodium hydride (60% dispersion in mineral oil) (50.4 mg, 1.26 mmol) in dry DMF (1.5 ml) in a pre-dried round bottomed flask was added [(2S)-1-methyl-2-pyrrolidiny]methanol (0.15 ml, 1.26 mmol) under an argon atmosphere. The resulting mixture was stirred at 40 °C for five minutes. A solution of 8-fluoro-3-

(phenylsulfonyl)quinoline (D2) (200 mg, 0.7 mmol) in dry DMF (2 ml) was added in one portion and the resulting mixture was stirred at 60 °C under argon for 15 hours. The mixture was applied to an Isolute Flash SCX column (5 g sorbent), washed with methanol, then the compound eluted with 10% ammonia in methanol. The residue was purified by flash chromatography (20 g silica gel) with a gradient of 10% methanolic ammonia in dichloromethane to give 8-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-3-(phenylsulfonyl)quinoline (E2a) as a yellow solid. ¹H NMR (CDCl₃) δ 9.27 (1H, d), 8.78 (1H, d), 8.00 (2H, dd), 7.55 (5H, m), 7.21 (1H, dd), 4.23 (1H, dd), 4.08 (1H, dd), 3.14 (1H, dt), 2.93 (1H, m), 2.54 (3H, s), 2.33 (1H, m), 2.15 (2H, m), 1.85 (2H, m).

Example 2b

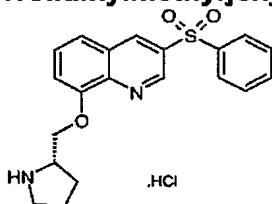
8-(((2S)-1-Methyl-2-pyrrolidinyl)methyl)oxy)-3-(phenylsulfonyl) quinoline, hydrochloride (E2b)



The free base was dissolved in methanol and transformed into the hydrochloride salt (E2b) by treating with HCl in Et₂O and stirring for 5 minutes followed by evaporation of the solvent. Mass spectrum: C₂₁H₂₂N₂O₃S requires 382; found 383 (MH⁺)

Example 3

3-(Phenylsulfonyl)-8-(((2S)-2-pyrrolidinylmethyl)oxy)quinoline, hydrochloride (E3)



To a suspension of sodium hydride (60% dispersion in mineral oil) (36.4 mg, 0.91 mmol) in dry DMF (1.5 ml) in an oven dried round bottomed flask was added (2S)-2-pyrrolidinylmethanol (0.09 ml, 0.91 mmol) under argon atmosphere and the resulting mixture was stirred at 40 °C for five minutes. A solution of 8-fluoro-3-(phenylsulfonyl)quinoline (D2) (200 mg, 0.7 mmol) in dry DMF (2 ml) was added in one portion and the resulting mixture was stirred at 60 °C under argon over 15 hours. The mixture was applied to an Isolute Flash SCX column (5g sorbent), washed with methanol then eluted with 10% ammonia in methanol. The crude material was purified by flash chromatography (20 g silica gel) with a gradient of 10% methanolic ammonia in dichloromethane to afford 3-(phenylsulfonyl)-8-(((2S)-2-pyrrolidinylmethyl)oxy)quinoline.

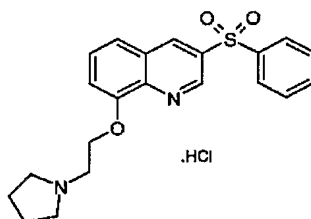
^1H NMR (CDCl_3) δ 9.26 (1H, d), 8.77 (1H, d), 8.02 (2H, dd), 7.54 (5H, m), 7.22 (1H, dd), 4.17 (1H, dd), 4.08 (1H, dd), 3.74 (1H, m), 3.01 (2H, m), 2.01 (1H, m), 1.86 (2H, m), 1.61 (1H, m).

This material was dissolved in methanol and transformed into the hydrochloride salt (E3) a yellow solid, by treating with HCl (1M in Et_2O , 0.7 ml) and stirring for 5 minutes followed by evaporation of the solvent.

Mass spectrum: $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ requires 368; found 369 (MH^+)

Example 4

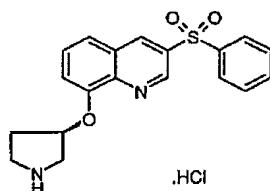
10 3-(Phenylsulfonyl)-8-[[2-(1-pyrrolidinyl)ethyl]oxy]quinoline, hydrochloride (E4)



This compound was prepared in a similar manner to the methods of Example E1a and Example E1b but using 2-(1-pyrrolidinyl)ethanol in place of 2-dimethylaminoethanol, affording 3-(phenylsulfonyl)-8-[[2-(1-pyrrolidinyl)ethyl]oxy]quinoline, hydrochloride (E4). Mass spectrum: $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ requires 382; Found 383 (MH^+)

Example 5

20 3-(Phenylsulfonyl)-8-[(3R)-3-pyrrolidinyl]oxy]quinoline, hydrochloride (E5)



A suspension of sodium hydride (60% oil dispersion, 43mg) in DMF (2mL), was treated dropwise with a solution of 1,1-dimethylethyl (3R)-3-hydroxy-1-pyrrolidinecarboxylate (1.81 mmol, 338 mg) in DMF (3 mL) and the mixture stirred for 10 minutes. The resulting solution was treated with 8-fluoro-3-(phenylsulfonyl)quinoline (D2) (400 mg, 1.39 mmol) in DMF (5 mL). The mixture was heated to 60°C for 16h, then cooled, poured into dichloromethane (70 mL), washed with water (50 mL) then brine (50 mL), dried (MgSO_4) and evaporated to afford a brown oil (764 mg). This was purified by silica gel chromatography (50 g cartridge) eluting with a linear gradient of increasing ethyl acetate in pentane to give 1,1-dimethylethyl (3R)-3-[[3-(phenylsulfonyl)-8-quinolinyl]oxy]-1-pyrrolidinecarboxylate (426 mg). This was treated with hydrogen chloride in 1,4-dioxane (4M, 5 mL) for two hours then the solvent removed *in vacuo*. The residue was further purified by preparative reverse phase chromatography, and the resulting material by normal phase chromatography on silica gel eluting with dichloromethane and an

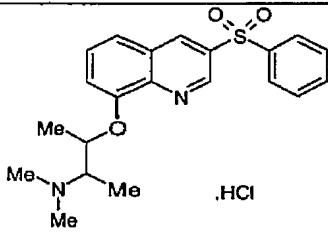
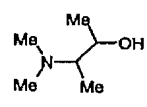
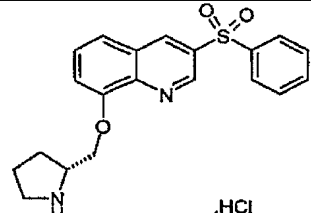
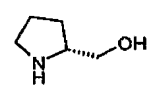
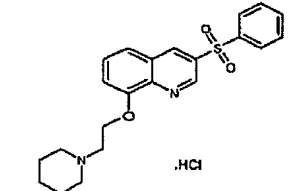
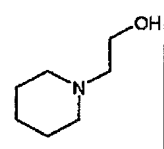
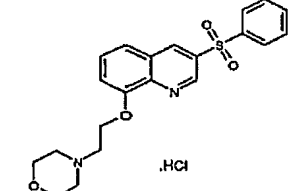
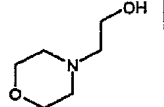
increasing gradient of 10% aqueous ammonia in methanol. The resulting solid was treated with methanol (2 mL) and hydrogen chloride in diethyl ether (1M, 1 mL) followed by evaporation to give 3-(phenylsulfonyl)-8-[(3*R*)-3-pyrrolidinyloxy]quinoline, hydrochloride (E5).

5 Mass spectrum: $C_{19}H_{18}N_2O_3S$ requires 354; found 355 (MH^+)

Examples 6-13 (E6-E13)

Examples 6-13 were prepared in a similar manner to the procedure described in Example 1, or Example 3, from the corresponding hydroxyalkylamine indicated in the table below:

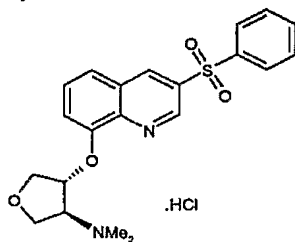
10

Example	Structure	Hydroxyalkyl -amine	Compound Name	Analogous Method to	Mass Spectrum
E6			Dimethyl(1-methyl-2-[(3-(phenylsulfonyl)-8-quinolinyloxy)propyl]amino)ethanol hydrochloride	E3	Requires 384; Found 385 (MH^+)
E7			3-(Phenylsulfonyl)-8-[(2 <i>R</i>)-2-pyrrolidinylmethyl]oxyquinoline, hydrochloride	E3	Requires 354; Found 355 (MH^+)
E8			3-(Phenylsulfonyl)-8-[(2-(1-piperidinyloxy)ethyl]oxyquinoline, hydrochloride	E1	Requires 396; Found 397 (MH^+)
E9			8-[(2-(4-morpholinylethyl)oxy)-3-(phenylsulfonyl)]quinoline, hydrochloride	E1	Requires 398; Found 399 (MH^+)

Example	Structure	Hydroxyalkyl -amine	Compound Name	Analogous Method to	Mass Spectrum
E10			8-(1-Azabicyclo[2.2.2]oct-3-yloxy)-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 394; Found 395 (MH ⁺)
E11			3-(Phenylsulfonyl)-8-([3-(1-piperidinyl)propyl]oxy)quinoline, hydrochloride	E3	Requires 410; Found 411 (MH ⁺)
E12			8-([2-(Hexahydro-1H-azepin-1-yl)ethyl]oxy)-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 410; Found 411 (MH ⁺)
E13			((3S,4R)-4-([3-(Phenylsulfonyl)-8-quinolinyloxy]tetrahydro-3-furanyl)amine, hydrochloride	E3	Requires 370; Found 371 (MH ⁺)

Example 14

(3S,4R)-N,N-Dimethyl-4-([3-(phenylsulfonyl)-8-quinolinyloxy]tetrahydro-3-furanamine, hydrochloride (E14)



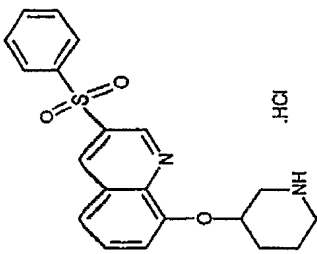
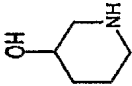
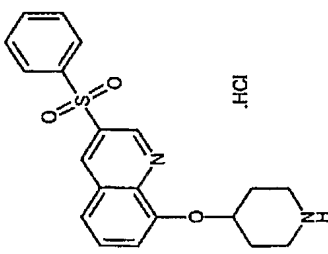
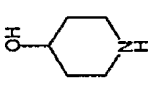
5

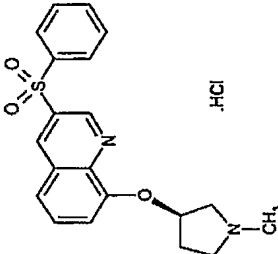
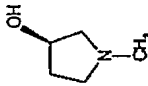
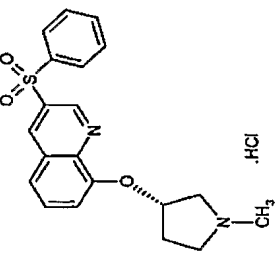
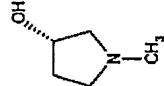
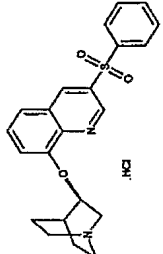

The free base form of ((3S,4R)-4-([3-(phenylsulfonyl)-8-quinolinyloxy]tetrahydro-3-furanamine, hydrochloride (E14)

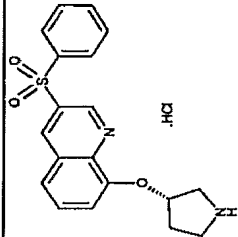
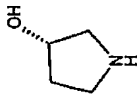
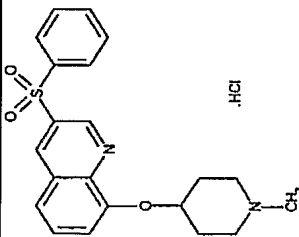
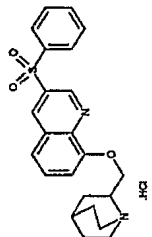

5 tetrahydro-3-furanyl)amine, from Example E13 (60 mg) was treated with formalin (37% formaldehyde in water, 0.2 mL), in 1,2-dichloroethane (3 mL) and sodium triacetoxyborohydride (137 mg) added. The mixture was stirred for 18 hours then filtered through an SCX cartridge (10g), eluting with methanol then 10% aqueous ammonia in methanol to afford a yellow paste. This was treated with hydrogen chloride in methanol (1M), to give, after evaporation, (3S,4R)-N,N-dimethyl-4-[[3-(phenylsulfonyl)-8-quinolinyl]oxy]tetrahydro-3-furanamine, hydrochloride (E14)
Mass spectrum: $C_{21}H_{22}N_2O_4S$ requires 398; Found 399 (MH^+)

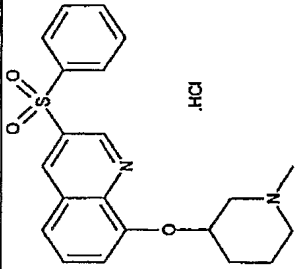
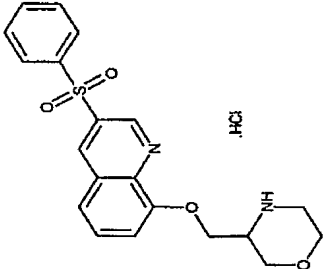
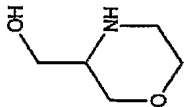
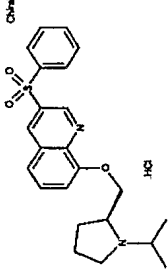
10 **Examples 15-26 (E15-E26)**

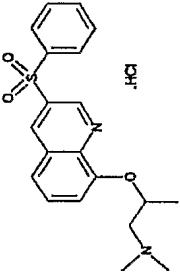
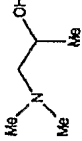
Examples 15-26 were prepared either in a similar manner to the procedure described in Example 3 from the corresponding hydroxyalkylamines in the table below, or in a similar manner to the procedure described in Example 14 using the carbonyl compounds and parent amines from Example numbers indicated in the table below.

Example	Structure	Hydroxyalkyl -amine	Carbonyl Compound and Parent Amine Example	Compound Name	Analogous Method to	Mass Spectrum
E15			-	3-(Phenylsulfonyl)-8-(3-piperidin-1-yl-oxy)quinoline, hydrochloride	E3	Requires 368; Found 369 (MH ⁺)
E16			-	3-(Phenylsulfonyl)-8-(4-piperidin-1-yl-oxy)quinoline, hydrochloride	E3	Requires 368; Found 369 (MH ⁺)

Example	Structure	Hydroxyalkyl-amine	Carbonyl Compound and Parent Amine Example	Compound Name	Analogous Method to	Mass Spectrum
E17			-	8-[[[(3R)-1-Methyl-3-pyrrolidinyl]oxy]-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 368; Found 369 (MH ⁺)
E18			-	8-[[[(3S)-1-Methyl-3-pyrrolidinyl]oxy]-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 368; Found 369 (MH ⁺)
E19			-	8-[(3R)-1-Azabicyclo[2.2.2]oct-3-yloxy]-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 394; Found 395 (MH ⁺)

Example	Structure	Hydroxyalkyl -amine	Carbonyl Compound and Parent Amine Example	Compound Name	Analogous Method to	Mass Spectrum
E20			-	3-(Phenylsulfonyl)-8- [(1S)-3-pyrrolidinyl]oxy] quinoline, hydrochloride	E3	*
E21		-	Formalin E16	8-[(1-Methyl-4- piperidinyl)oxy]-3- (phenylsulfonyl) quinoline, hydrochloride	E14	Requires 382; Found 383 (MH ⁺)
E22			-	8-[(1- Azabicyclo[2.2.2]oct-2- yl)methyl]oxy]-3- (phenylsulfonyl) quinoline, hydrochloride	E3	Requires 408; Found 409 (MH ⁺)

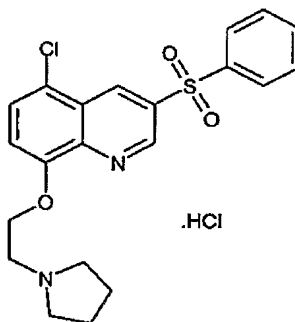
Example	Structure	Hydroxyalkyl -amine	Carbonyl Compound and Parent Amine Example	Compound Name	Analogous Method to	Mass Spectrum
E23		-	Formalin E15	8-[(1-Methyl-3-piperidinyl)oxy]-3-(phenylsulfonyl)quinoline, hydrochloride	E14	Requires 382; Found 383 (MH ⁺)
E24			-	8-[(3-Morpholinylmethyl)oxy]-3-(phenylsulfonyl)quinoline, hydrochloride	E3	Requires 384; Found 385 (MH ⁺)
E25		-	Acetone E3	8-[(2S)-1-(1-Methylethyl)-2-pyrrolidinylmethyl]oxy)-3-(phenylsulfonyl)quinoline, hydrochloride	E14	Requires 410; Found 411 (MH ⁺)

Example	Structure	Hydroxyalkyl -amine	Carbonyl Compound and Parent Amine Example	Compound Name	Analogous Method to	Mass Spectrum
E26			-	N,N-Dimethyl-2-[[3-(phenylsulfonyl)-8-quinolinyloxy]-1-propanamine, hydrochloride	E3	Requires 370; Found 371 (MH ⁺)

*For E20: ^1H NMR (CD_3OD): 2.30-2.45 (m, 2H), 3.67-3.73 (m, 1H), 3.84-3.92 (m, 2H), 4.02-4.15 (m, 1H), 5.50-5.54 (m, 1H), 7.64-7.72 (m, 2H), 7.85 (d, $J = 7\text{Hz}$, 1H), 7.95-8.05 (m, 2H), 8.10-8.20 (m, 2H), 8.23 (d, $J = 9\text{Hz}$, 1H), 9.45 (br s, 1H), 9.76 (br s, 1H).

Example 27

5-Chloro-3-(phenylsulfonyl)-8-[[2-(1-pyrrolidinyl)ethyl]oxy]quinoline hydrochloride (E27)



10

To a stirred solution of 3-(phenylsulfonyl)-8-[[2-(1-pyrrolidinyl)ethyl]oxy]quinoline (0.1g, 0.26mmol) in acetic acid (2mL) was added N-chlorosuccinimide (38mg, 0.29mmol) in a single portion and the resulting mixture heated to 100°C for 18h. After allowing to cool to ambient temperature, the reaction mixture was concentrated *in vacuo* followed by purification by preparative HPLC. The resulting material was treated with 1M HCl/E₂O to afford the title compound as a beige solid (35mg). Mass spectrum: C₂₁H₂₁N₂O₃SCl Requires 416/418; Found 417/419 (MH⁺)

20 Pharmacological data

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following cyclase assay:

Cyclase Assay

25 0.5μl of test compound in 100% dimethylsulfoxide (DMSO) was added to a white, solid 384 well assay plate (for dose response measurements the top of the concentration range is 7.5μM final). 10μl of washed membranes of HeLa 5HT₆ cells (for preparation see WO 98/27081) in basic buffer (50mM HEPES pH 7.4 (KOH), 10mM MgCl₂, 100mM NaCl, 1μl/ml 3-isobutyl-1-methylxanthine (IBMX) (Sigma-Aldrich)) was added to all wells
30 followed by 10μl 2 x ATP buffer (100μl/ml ATP and 1μl/ml 3-Isobutyl-1-methylxanthine (IBMX) (Sigma-Aldrich)) with 5-HT (at a concentration equivalent to a dose response of 4 x EC₅₀). The resultant mixture was then incubated at room temperature for 30-45 minutes to allow cAMP production.

35 cAMP production was then measured using the DiscoverX™ HitHunter™ chemiluminescence cAMP assay kit (DiscoverX Corporation, 42501 Albrae Street,

Fremont, CA 94538; Product Code: 90-0004L) or any other suitable cAMP measurement assay.

- 5 IC_{50} values were estimated from arbitrary designated unit (ADU) measurements from a Perkin Elmer Viewlux instrument using a four parameter logistic curve fit within EXCEL (Bowen, W.P. and Jerman, J.C. (1995), Nonlinear regression using spreadsheets. *Trends in Pharmacol. Sci.*, **16**, 413-417). Functional K_i values were calculated using the method of Cheng, Y.C. and Prusoff, W.H. (Biochemical Pharmacol (1973) **22** 3099-3108). pIC_{50} and fpK_i are the negative log10 of the molar IC_{50} and functional K_i
- 10 respectively.

- The compounds of Examples E1b, E2b and E3-E27, were tested in the above cyclase assay. Compounds of Examples E1b, E2b, E3-E7, E15, E17 and E22-E24 showed antagonist potency for the 5-HT₆ receptor, having fpK_i values > 8.0 at human cloned 5-
- 15 HT₆ receptors. The compounds of all other Examples also showed antagonist potency for the 5-HT₆ receptor, having fpK_i values ≥ 7.0 and < 8.0 at human cloned 5-HT₆ receptors.